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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): 4133-031323

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on August 9, 2006

Signature: [signature]

Typed or printed name: Lisa R. McNany

Application Number	Filed
10/736,489	12/15/2003

First Named Inventor: Xia Zhao

Art Unit	Examiner
1744	Monzer R. Chorbaji

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- [ ] applicant/inventor.
- [ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- [x] attorney or agent of record. Registration number 37,891
- [ ] attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

[signature]
Signature

Kirk M. Miles
Typed or printed name

412-471-8815
Telephone number

August 9, 2006
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

- [ ] *Total of _____ forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	10/736,489	Confirmation No.	:	3805
Applicant	:	Xia Zhao et al.			
Filed	:	December 15, 2003			
Title	:	TERMINAL STERILIZATION OF PREFILLED CONTAINERS			
Art Unit	:	1744			
Examiner	:	Monzer R. Chorbaji			
Customer No.	:	32182			

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Sir:

For the reasons set forth herein, Applicants respectfully submit that the final Office Action is based upon improper rejections of the claims and fails to establish a *prima facie* case of obviousness based on the cited references.

I. Rejection of claims 1, 17, and 32 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,231,936 to Kozimor et al. in combination with the admitted state of the prior art.

The present invention is generally directed to the unexpected and surprising finding that the radiation sterilization of a container constructed of polyolefin including a radiation stabilizer will have less of an adverse impact on the contents of the container if the container is prefilled with a medium prior to subjecting the container to a gamma radiation treatment.

It is well known to construct containers useful as medical devices, and particularly syringes, out of polyolefin materials. Polyolefin is particularly useful in such applications due to its ease of manufacture and inexpensive raw materials. However, polyolefin materials such as polypropylene are not very resistant to the softening effects and the degradation

that occurs when such materials are subjected to sterilizing dosages of ionizing radiation, particularly gamma radiation. As a result, irradiation of polyolefin containers causes the generation of highly reactive species. Through the present invention it has been discovered that such species can alter the contents of the container, and that the generation of these species can be inhibited in order to prevent degradation of the medium contained within the container in order to meet the European and/or U.S. Pharmacopoeia requirements for such mediums.

In particular, the present invention provides the unexpected finding that the integrity of a medium contained within a container can be maintained within an acceptable useful range, with the level of oxidizable substances within the medium maintained below about 3.4 ppm, by using radiation stable polyolefins in combination with gamma irradiation, and by ensuring that the container is filled with the medium prior to such gamma irradiation treatment. The present inventors have discovered that a synergy exists between the composition of the container, the type of sterilization treatment such as gamma irradiation, and the requirement that a medium be present within the container prior to the gamma irradiation. Specifically, it has now been discovered that prefilling the container prior to irradiation provides a medium to neutralize the radical reactions during irradiation, thus minimizing the reactions which incorporate radical scavengers, i.e. oxidizable substances, such as hydrogen peroxide. In other words, the present invention provides a useful product by inhibiting any adverse reaction of the contents of the prefilled container during radiation sterilization treatment from occurring.

The final Action alleges that Kozimor teaches a radiation stable, prefilled container that is to be sterilized by gamma irradiation after being filled with a medium and that such a teaching, combined with the suggestion that it is desirable to have less than 3.4 ppm of oxidizable substances in the medium after radiation sterilization, renders the present invention obvious. In order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one skilled in the art, to modify the reference or combine reference teachings, and there must be a reasonable likelihood of success in doing so. *See* MPEP §2143. Because there is no suggestion or motivation to modify or combine the references in such a way, or more directly that there would be success in doing so, there is a clear deficiency in the *prima facie* case in support of this rejection.

The cited references fail to teach or even suggest that the contents of a container may be affected based on whether the container is filled or unfilled prior to a gamma radiation treatment. In particular, nothing in Kozimor even remotely suggests that prefilling the container prior to radiation treatment will achieve such results. In response, the Examiner contends in the Advisory Action that "Kozimor explicitly teaches that prefilled containers will undergo gamma irradiation sterilization step", and that "the benefit of maintaining oxidizable substances after radiation to below 3.4 ppm is disclosed in the admitted state of the prior art...." The Examiner then concludes that "one or ordinary skill in the art upon reading Kozimor and European Pharmacopoeia requirements would recognize this benefit by preventing the oxidizable substances to go over 3.4 ppm after gamma radiation treatment." The Examiner, however, fails to demonstrate in any way how one skilled in the art would recognize how to achieve the benefit of maintaining the oxidizable substances below such a limit. Kozimor does not distinguish between sterilization methods, and fails to even recognize that the type of sterilization, or whether the container is filled or empty prior to sterilization, could have an effect on such properties. The mere fact that the Pharmacopoeia standards require a certain property does not correct the deficient teachings of Kozimor. There is nothing in Kozimor which would lead one skilled in the art to recognize that filling the container prior to subjecting it to radiation will reduce the level of oxidizable substances.

In fact, Kozimor discloses that the syringes taught therein can be filled either before or after irradiation. *See* Kozimor, col. 4, lines 13-15. Such disclosure actually teaches away from the present invention, since it has now been discovered that filling the container prior to irradiation reduces the level of oxidizable substances within the medium compared to the situation where the container is filled after irradiation. This distinction, as well as the unexpected and beneficial results of the present invention, is demonstrated by the comparative data in Examples 3 and 4 of the present disclosure. Example 3 demonstrates the unexpected result that when syringes, constructed of a radiation stable polyolefin polymer, are filled with a sample medium prior to the irradiation step there is a marked improvement in sample quality when compared to syringes which were irradiated and then filled. Example 4 demonstrates that the type of radiation treatment in a terminal sterilization process is important to product quality

since gamma irradiation reduces the amount of oxidizable materials in a sample to a greater extent than E-beam irradiation.

The Examiner fails to identify where in the references it is suggested that the irradiation treatment should occur only after the container is filled, and that doing so will successfully result in a reduction in the oxidizable substances present within the medium. As previously noted, Kozimor teaches away from this suggestion by allowing for syringes to be filled before or after sterilization without suggesting that one option is more desirable than the other. The Examiner also fails to identify any evidence in the references that would suggest to one skilled in the art that the type of radiation treatment has an effect on the amount of oxidizable materials in the sample, as now discovered through the present invention. This synergistic effect is realized only through the present invention through the specific sterilization treatment with the container filled in a specific manner. The existence of standard pharmacopoeia requirements does nothing to cure these deficiencies, but instead only suggests one possible benefit of maintaining a low level of such substances. The Examiner fails to indicate why one skilled in the art, having knowledge of these requirements, would know to modify the Kozimor teachings in such a way that the polyolefin containers taught therein would undergo gamma radiation only after being filled with a medium and that doing so would successfully inhibit the adverse reactions on the enclosed medium so the level of oxidizable substances in the medium is below 3.4 ppm.

Based on these remarks, a *prima facie* case of obviousness of the independent claims 1, 17, and 32 has not been made since the Examiner has failed to establish any suggestion or motivation to modify or combine the prior art teachings which would render the present invention obvious, or that there would be a reasonable likelihood of success in doing so. As such, the rejections are improper and should be withdrawn.

II. Rejection of the dependent claims under 35 U.S.C. §103(a) based on Kozimor in view of additional references.

The final Action recites a number of additional rejections of the dependent claims under 35 U.S.C. §103(a) based on Kozimor alone or in view of additional references.

As discussed in detail above, Kozimor fails to teach or suggest prefilling a syringe prior to sterilizing the syringe with gamma irradiation, and the additional references do not cure this deficiency. Jacobs has been cited for teaching gamma irradiation of a saline water medium with a medium pH of 5.0 after irradiation. Williams has been cited for teaching the inclusion of a clarifying agent such as dibenzylidene sorbitol alkyl thioether, a mobilizing additive such as a hydrocarbon oil, and a stabilizer of bis (4-piperidinyl) diester of a dicarboxylic acid within the container composition. Saito et al. have been cited for teaching the inclusion of a nucleating agent such as 2,2'-methylene-bis (4,6-di-t-butylphenol) phosphate salt. None of these references correct the deficiencies in the Kozimor reference, namely that filling the syringe prior to sterilization by gamma radiation inhibits adverse reaction of the contents of the container. Accordingly, Applicants submit that these rejections be withdrawn.

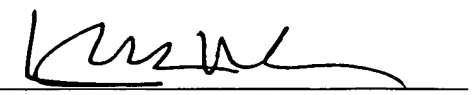
III. Conclusion

Based upon the above specified clear errors and deficiencies, Applicants assert that the Examiner has failed to establish a *prima facie* case of obviousness. It is therefore respectfully requested that the final rejections be withdrawn and reversed and that all pending claims, in their current form, be allowed.

Any questions regarding this submission should be directed to Applicants' undersigned representative, who can be reached by telephone at 412-471-8815.

Respectfully submitted,

THE WEBB LAW FIRM

By 

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